continue therapy with cholestyramine after many years of administration.

REFERENCES

1. Riely C, Collier E, Jensen P, et al: Arteriohepatic dysplasia: A benign syndrome of intrahepatic cholestasis with multiple organ involvement. Ann Intern Med 91:520-527, Oct 1979
2. Watson DH, Miller V: Arteriohepatic dysplasia. Arch Dis Child 48:459-466, Jun 1973
3. Alagille D, Odièvre M, Gautier M, et al: Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental and sexual development and cardiac murmur. J Pediatr 86:63-71, Jan 1975
4. Alagille D, Habib EC, Thomassin N: L'atrésie des voies biliaires intrahépatiques avec voies biliaries extrahépatiques permeables chez l'enfant. Journees Paris Pediatr pp 301-318, 1969
5. Alagille D, Thomassin N: L'atrésie des voies biliares intrahépatiques avec voies biliaires extrahépatiques permeables chez l'enfant. Rev Med Chir Mal Foie 45:93-104, 1970
6. Greenwood RJ, Rosenthal A, Crocker A, et al: Syndrome of intrahepatic biliary dysgenesis and cardiovascular malformations. Pediatrics 58:243-247, Aug 1976
7. Henriksen M, Langmark F, Sorland S, et al: Hereditary cholestasis combined with peripheral pulmonary stenosis and other anomalies. Acta Paediatr Scand 66:7-15, Jan 1977
8. Ahrens, EH Jr, Harris RC, MacMahon HE, et al: Atresia of the intrahepatic bile ducts. Pediatrics 8:628-647, Nov 1951
9. Lottsfeldt FI, Knivit W, Aust JB, et al: Cholestyramine therapy in intrahepatic biliary atresia. N Engl J Med 269:186-189, Jul 25, 1963

Refer to: Shragg TA, Albertson TE, Fisher CJ Jr: Cyanide poisoning after bitter almond ingestion. West J Med 136:65-69, Jan 1982

Cyanide Poisoning After Bitter Almond Ingestion

THOMAS A. SHRAGG, MD
TIMOTHY E. ALBERTSON, MD, PhD
CHARLES J. FISHER, Jr, MD
Sacramento, California

ACUTE CYANIDE POISONING occurs relatively infrequently.[1] With the increasing use of amygdalin (commonly known as Laetrile) and other cyanogenic glycosides for alternative cancer therapy, accidental cyanide poisoning may become more common. Because of its rapid onset and the highly lethal nature of cyanide, many patients die before getting medical care.[1] Unfortunately, even when patients do obtain medical care the correct diagnosis is often delayed until well into their hospital course.[2,3] In reporting a case of cyanide poisoning, Graham and colleagues[2] noted the paucity of cases in which cyanide blood levels had been reported. They further questioned the efficacy and safety of the traditional therapy of intravenous sodium nitrite and sodium thiosulfate. We have recently treated a severe case of cyanide poisoning in which cyanide blood levels and the response to therapy were well documented.

ABBREVIATIONS USED IN TEXT

$A\text{-}aO_2$ = alveolar-arterial difference in oxygen
CVP = central venous pressure
FIO_2 = fraction of inspired oxygen
PCWP = pulmonary capillary wedge pressure
$\dot{Q}s/\dot{Q}t$ = right-to-left intrapulmonary shunt
SEM = standard error of the mean
$T_{1/2}$ = cyanide half-life in blood

Report of a Case

A 67-year-old woman weighing 60 kg (132 lb) was diagnosed as having carcinoma of the large bowel a year before the hospital admission described in this report. The tumor was judged to be resectable, but the patient refused either surgical therapy or consideration of chemotherapy. Eight months before admission to hospital, for a two-month period she self-administered injectable Laetrile purchased in Mexico. Subsequently, because of the expense of the injectable form, the patient switched to Laetrile tablets. The tablets were taken erratically but probably on an average of every other day over the next six months. Two weeks before the onset of her present illness, the patient was given a bag of bitter almonds by a friend, allegedly to help increase her "protein intake" and also for "medicinal purposes." Initially she ground up four to five bitter almonds and mixed them with water. Approximately 30 to 45 minutes after ingestion of the mixture, she became light-headed, and had nausea and vomiting with crampy abdominal pains. The symptoms subsided over the course of the evening and she felt well the next morning. On the night of admission she again made a slurry of water with 12 bitter almonds. She experienced a severe bout of crampy abdominal pain within 15 minutes after ingestion. The patient went into her bathroom and collapsed. Her daughter quickly called for an ambulance and en route to the hospital, a blood sample was taken and naloxone hydrochloride and 50 percent dextrose solution were administered, but failed to produce a response.

On arrival in the emergency room, the patient

From the Section of Critical Care/Emergency Medicine, Department of Internal Medicine, and the UCD Medical Center Regional Poison Center, University of California, Davis, Medical Center, Sacramento.

Submitted, revised, March 6, 1981.

Reprint requests to: C. J. Fisher, Jr., MD, Section of Critical Care/Emergency Medicine, Department of Internal Medicine, University of California, Davis, Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817.

TABLE 1.—*Blood Gas Measurements Following Cyanide Ingestion and Treatment With Sodium Nitrite and Sodium Thiosulfate*

Duration From Time of Nitrite and Thiosulfate Treatment	Arterial Blood Gas				Serum Lactate	A-aO_2	PCWP	CVP	$\dot{Q}s/\dot{Q}t$
	FIO_2 %	PaO_2 mm Hg	$PaCO_2$ mm Hg	pH	mEq/L	mm Hg	mm Hg	cm H_2O	%
−18 min	21	71	13	7.34	14.3	63	..	..	..
0 min	6 liters (mask)	56	25	7.17	..	..	..	..	..
23 min	50 (intubated)	63	19	7.41	..	270	..	..	..
1 hr	100	262	32	7.35	..	411	..	..	..
5 hr 25 min	100	257	30	7.47	1.7	419	10	10	..
7 hr 25 min	100	203	25	7.56	..	479	..	..	..
7 hr 25 min (mixed venous)		39	30	7.52	..	..	..	12	40
9 hr 35 min	60	102	22	7.59	1.0	298	..	8	..
9 hr 35 min (mixed venous)		37	25	7.57	..	..	..	..	30
11 hr 25 min	60	194	25	7.53	.9	203	..	..	..
18 hrs	21 (extubated)	56	35	7.49	1.0	50	..	..	..
36 hrs	21	106	30	7.45	..	7	..	..	..

A-aO_2 = alveolar-arterial difference in oxygen; PCWP = pulmonary capillary wedge pressure; $\dot{Q}s/\dot{Q}t$ = right-to-left intrapulmonary shunt; CVP = central venous pressure; FIO_2 = fraction of inspired oxygen.

was totally unresponsive to verbal command or painful stimuli and was incontinent of stool. The odor of bitter almonds was detected by some observers. Her blood pressure was 138/90 mm of mercury, pulse was 128 per minute and respirations were 20 per minute and deep. Oxygen was administered by mask and one ampule of amyl nitrite was given per inhalation. Sodium nitrite (300 mg) and then 12.5 grams of sodium thiosulfate (cyanide treatment kit, Eli Lilly Co.) were given intravenously. The patient was intubated for airway protection and oxygenation. Using a large-bore tube, her stomach was lavaged until it returned clear fluid. An initial gastric lavage specimen was sent to the laboratory for qualitative analysis and a later report showed it to be 4+ positive for the presence of cyanide. A cathartic of 48 grams of sodium biphosphate and 18 grams of sodium phosphate per dl (Fleet's Phospho-Soda) and 30 grams of activated charcoal were administered through the gastric tube. Within 20 minutes of receiving the cyanide antidote, the patient became alert and responded appropriately to verbal commands. A Swan-Ganz catheter was inserted and she was monitored for the next 24 hours in the intensive care unit and treated with mechanical ventilation. On x-ray studies of the chest transient bilateral pulmonary infiltrates associated with hypoxic respiratory failure were seen. Her pulmonary status improved concomitant with clearing of her chest on roentgenogram and she was extubated after 18 hours.

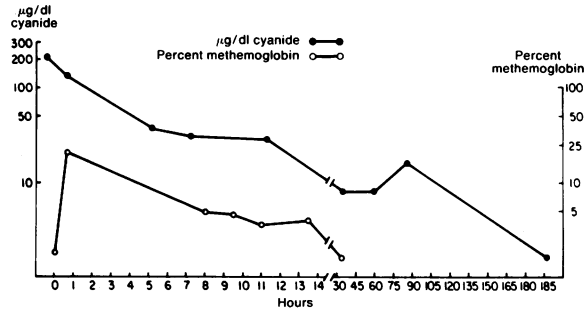

Figure 1.—Blood cyanide levels and percentage of methemoglobin are plotted against time following initiation of amyl nitrite, sodium nitrite and sodium thiosulfate treatment. The first blood specimen for cyanide level determination was drawn 20 minutes (time 0) before treatment began.

Table 1 shows arterial blood gas determinations, serum lactate levels, and the alveolar-arterial difference of oxygen (A-aO_2), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and right-to-left intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) obtained during her hospital stay. Cyanide and methemoglobin levels before and after treatment are displayed in Figure 1.

The remaining Laetrile tablets and bitter almonds were analyzed by Dr. Eric Conn, Department of Biochemistry, University of California at Davis. The Laetrile tablets weighed approximately 250 mg with an average amygdalin content (6 percent cyanide)[4] of 11.5 mg (±0.4 standard error of the mean [SEM]). The average weight of the bitter almonds was 1.32 grams (N = 5, ±0.04

SEM). The average cyanide content was 6.2 mg per each bitter almond (N=5, ±0.3 SEM) or approximately 469 mg per 100 grams of bitter almonds.

Discussion

This is a case of severe cyanide intoxication after bitter-almond ingestion, complicated by lactic acidosis and pulmonary edema, that dramatically responded to aggressive supportive care and treatment with sodium nitrite and sodium thiosulfate. Graham and his colleagues[2] recently described another case of cyanide poisoning associated with lactic acidosis and pulmonary edema. They felt the level of lactic acidosis correlated with the severity of cyanide poison and could be explained by the histotoxic hypoxia associated with the cyanide poisoning. Our patient had an initial serum lactate level of 14.3 mEq per liter, which fell with therapy to a level of 1.7 mEq per liter, suggesting a substantial degree of cyanide poisoning. Further, Graham and co-workers speculated on several possible causes for the pulmonary edema but concluded that the toxic effect of potassium cyanide on the myocardium would lead to cardiac failure and high-pressure pulmonary edema. We measured PCWP in our patient and found no evidence of increased left ventricular filling pressures. Berlin[5] has suggested a central neurogenic mechanism in the previously reported case of cyanide-induced pulmonary edema. Initially our patient had an A-aO_2 of 63 mm of mercury, which subsequently rose to 270 mm of mercury on 50 percent fraction of inspired oxygen (FIO_2). Her inital $\dot{Q}s/\dot{Q}t$ was 40 percent with a PCWP of 10 mm of mercury. We believe our patient had pulmonary edema from altered capillary permeability. This may be the result of the toxic effect of cyanide directly on capillary endothelium or an indirect neurogenic effect leading to increased pulmonary capillary permeability.[6]

Morse and associates[7] have warned that with the increasing publicity about Laetrile, consumption of cyanogenic glycoside-containing seeds as a substitute may increase. Cyanogenic glycosides have been found in approximately 150 plant species.[8] Amygdalin, probably the best known of the cyanogenic glycosides, was first isolated from the seeds of the bitter almond.[9] Amygdalin is also present in the kernels of stone fruits such as apricots, cherries and plums.[8,9,12] The cyanogenic glycoside content within a particular type of plant may vary. Several investigators have suggested that the cyanide content of apricot pits is affected by soil conditions, watering practices and when the fruit was harvested.[8,11,12] The toxicity of amygdalin is directly attributable to the release of hydrogen cyanide. This release of cyanide occurs by mild acid hydrolysis or through the action of enzymes (β-glucosidase or emulsion) that can be found in the seeds.[9,13,14] Amygdalin yields glucose, benzaldehyde and cyanide when hydrolyzed.[14] The enzymes are not found in mammalian tissues but have been isolated from the microflora found in human intestine.[1] This probably explains why amygdalin is more than 40 times more toxic when taken orally than when taken by intravenous injection.[1]

Animal poisoning by cyanide-containing fruits and grasses has long been recognized as a problem in veterinary medicine.[15] The extent of accidental cyanogenic glycoside poisoning in humans is not known. However, there have been numerous reports of cyanide poisoning in humans from apricot pits.[11,14,16] Sayre and Kaymakcalan[14] found that the average cyanide content in the popular wild apricot seed in Turkey was 217 mg per 100 grams. This is less than half the amount of cyanide that we found in these bitter almonds. Cyanide poisoning from bitter almonds has been reported rarely.[17,18] The cyanide content found in this case of 6.2 mg per almond is similar to the 4 to 9 mg of cyanide per almond previously reported.[19]

Edwards and Thomas[3] reported the case of a 48-year-old chemist who was resuscitated after being found asystolic following the ingestion of cyanide. The cyanide level in the blood in this case of near-lethal ingestion was found to be 380 μg per dl. Recently a patient taking Laetrile experienced weakness, lightheadedness, palpitations and headaches after taking twice his usual dose.[20] An unusually high cyanide level of 600 μg per dl was found in a single blood sample taken from this patient on an outpatient basis. Unfortunately, no follow-up data were available. Normal levels of cyanide in the blood have been reported to be 10 to 20 μg per dl.[21] Toxic levels are variable but are usually considered to be over 100 μg per dl.

A minimum lethal dose of cyanide has been estimated at 50 mg[22,23] or 0.5 mg per kg of body weight.[24] The calculated lethal dose based on the weight of the patient in this report would be 30 mg. From the number of almonds she reportedly ate, it is estimated that she ingested at least 70 to 75 mg of cyanide. The estimated amount of

cyanide ingested, the high level of cyanide in the blood, the strongly positive qualitative test on the gastric aspirate, and the drastic clinical condition of the patient when she arrived in the emergency department all strongly support a case of potentially lethal ingestion. Although the patient had been taking a cyanide-containing compound sporadically over the preceding eight months, her acute symptoms developed only on the two occasions when she ingested bitter almonds. This indicates acute rather than chronic poisoning.

The mechanism of cyanide poisoning has been well described.[4] Hydrogen cyanide interrupts the electron transport at the cytochrome *a* to cytochrome a_3 step. The resultant binding of cyanide to cytochrome oxidase inhibits cellular oxygen metabolism (histotoxic hypoxia), leading to cell death.

Treatment aims at decreasing the amount of cyanide available for cellular binding. Cyanide is rapidly absorbed from the gastrointestinal tract. Our patient was initially treated with both charcoal and phosphate-biphosphate after gastric lavage. Cyanide is poorly bound by charcoal, thus prevention of absorption by immediate gastric lavage or emesis is necessary.[25] The potential importance of gastric lavage can be seen in a report of a fatal case of bitter-almond poisoning, in which the stomach contents revealed a cyanide concentration of 4,380 μg per dl with the next highest concentration in the blood (312 μg per dl).[17]

Numerous antidotes for cyanide poisoning have been suggested over the years. In an 1888 report, Pedigo[26] first suggested the potential antagonism between amyl nitrite and "prussic acid" (hydrogen cyanide). He noted that amyl nitrite not only lengthened the survival period for dogs that had been given cyanide but also provided some prophylactic effect if administered before a cyanide injection. Geiger[27] later suggested the beneficial effects of methylene blue in the treatment of cyanide poisoning. Using dogs, Chen and coworkers[28] compared the antidotal effects of methylene blue, sodium thiosulfate, amyl nitrite, sodium tetrathionate and sodium nitrite given alone and in combinations. Chen and his colleagues concluded that "the highest antidotal action is exhibited by the combination of sodium nitrite and sodium thiosulfate." Chen and Rose[10] later reported that 43 of 44 patients were successfully treated with the combination of sodium nitrite and sodium thiosulfate. Unfortunately, they did not measure blood cyanide levels in any of their work to document the severity of the poisoning or the efficacy of treatment.

Sodium nitrite initially changes hemoglobin to methemoglobin, which binds cyanide. Methemoglobin can also reverse the cyanide inhibition of cytochrome oxidase activity in vitro by complexing with cyanide to form a cyanomethemoglobin compound.[29] Thiosulfate then combines with the cyanide-methemoglobin complex and a relatively nontoxic compound is then formed in the presence of rhodanese. The use of sodium nitrite is not without potential toxicity. Berlin[30] reported a case of a 17-month-old child who died as the result of massive sodium nitrite administration. The child was given 450 mg of sodium nitrite, producing a calculated methemoglobin level in excess of 90 percent. Bodansky[31] has estimated that blood concentrations of less than 30 percent methemoglobin produce no symptoms and that lethal levels must exceed 70 percent. Our patient received the recommended adult dosage of 300 mg of sodium nitrite. The resulting peak methemoglobin level of 21 percent was well below the symptomatic range.

Hydroxycobalamin has also been proposed as an antidote for cyanide poisoning.[32-34] It is thought to combine with cyanide to form cyanocobalamin (vitamin B_{12}).[32] Several cases of successful clinical application have been reported.[35] It offers the advantage of little toxicity and may be even more effective in combination with thiosulfate therapy.[36,37] However, hydroxycobalamin is not available in this country in a concentrated form.[38] The cobalt salts, cobalt chloride and ethylenediaminetetraacetate (EDTA), have also been used to form clinically useful complexes with cyanide, but these salts are also not available in this country.[22,36-38]

The importance of general supportive measures in cyanide poisoning including the administration of oxygen has been stressed previously.[22,39] Maxwell[20] has noted recently the lack of pharmacokinetic data after human cyanide poisoning. One case of cyanide poisoning reported three cyanide blood levels over a period of 84 hours.[2] The first level was drawn 12 hours after admission. From these data, we have been able to calculate an estimated cyanide half-life in blood ($T_{1/2}$) of 66 hours. Our patient appears to have had an initial elimination-phase $T_{1/2}$ of 2 hours and a terminal elimination-phase $T_{1/2}$ estimated at 44 hours (see Figure 1). Our patient rapidly and dramatically responded to treatment with oxygen, gastric lavage

and sodium nitrite followed by sodium thiosulfate. The rapid $T_{1/2}$ of the initial phase corresponded to the time when blood methemoglobin levels were also maximum. The sodium nitrite and sodium thiosulfate treatment may have contributed to this early rapid fall in cyanide levels. It would appear that our terminal elimination phase $T_{1/2}$ of 44 hours is similar to the long $T_{1/2}$ calculated from the cyanide blood levels drawn after 12 hours in the previous case.[2] The exact contribution to the prolonged terminal phase elimination kinetics of any delayed absorption of cyanide after distal intestinal breakdown is unknown.

Conclusion

There does not appear to be an ideal antidote for cyanide poisoning. This case illustrates the successful early diagnosis and treatment of a severe cyanide intoxication associated with lactic acidosis and permeability pulmonary edema after the ingestion of a lethal amount of bitter almonds. Aggressive supportive care and sodium nitrite followed by sodium thiosulfate was used. This case also demonstrates the need for frequent blood cyanide levels to document pharmacokinetics and any response to treatment. In addition to the need for further animal studies,[5] a multicenter study is needed to better evaluate the various cyanide antidote treatments alone and in combination.

REFERENCES

1. Smith RP: Toxic responses of the blood, chap 14, *In* Doull J, Klaassen CD, Amdur MD (Eds): Cassarett and Doull's Toxicology, 2nd Ed. New York, Macmillan Publishing, 1980

2. Graham DL, Laman D, Theodore J, et al: Acute cyanide poisoning complicated by lactic acidosis and pulmonary edema. Arch Intern Med 137:1051-1055, 1977

3. Edwards AC, Thomas ID: Letter to Editor. Lancet 1:92-93, Jan 1978

4. Klaassen CD: Nonmetallic environmental toxicants: Air pollutants, solvents and vapors, and pesticides, chap 70, *In* Gilman AG, Goodman LS, Gilman A (Eds): The Pharmacological Basis of Therapeutics, 6th Ed. New York, Macmillan Publishing, 1980, pp 1651-1652

5. Berlin C: Cyanide poisoning—A challenge. Arch Intern Med 137:993-994, 1977

6. Theodore J, Robin ED: Speculations on neurogenic pulmonary edema (NPE). Am Rev Resp Dis 113:405-411, 1976

7. Morse DL, Harrington JM, Heath CW: Laetrile, apricot pits, and cyanide poisoning. N Engl J Med 245:1264, 1976

8. Stoewsand GS, Anderson JL, Lamb RC: Cyanide content of apricot kernels. J Food Sci 40:1107, 1975

9. Lierner IE: Cyanogenetic Glycosides, National Research Council Publication No. 1354. National Academy of Science, pp 58-61, 1966

10. Chen KK, Rose CL: Nitrite and thiosulfate therapy in cyanide poisoning. JAMA 149:113-119, 1952

11. Gunder AE, Abrahamov A, Weisenberg E, et al: Cyanide poisoning in a child secondary to eating apricot pits. Harefuah 76:536-538, 1969

12. Montgomery RD: The medical significance of cyanogen in food stuffs. Am J Clin Nutr 17:103-112, 1965

13. György B, André L, Stehli L, et al: Direct potentiometric determination of cyanide in biological systems. Anal Chim Acta 46:318-321, Jul 1969

14. Sayre JW, Kaymakcalan S: Cyanide poisoning from apricot seeds among children in central Turkey. N Engl J Med 270:1113-1115, 1964

15. Couch JF: Poisoning of livestock by plants that produce hydrocyanic acid. US Department of Agricuture, Leaflet No. 88, Sep 1934

16. Yatziv A, Simcha S: Childhood cyanide poisoning secondary to eating apricot pits. Harefuah 76:535-536, 1969

17. Pack WK, Raudonat HW, Schmidt K: Lethal poisoning with hydrocyanic acid after ingestion of bitter almonds. Z Rechtsmed 70:53-54, 1972

18. Bonnischen R, Maehly AC: Poisoning by volatile compounds —III. Hydrocyanic acid. J Forensic Sci 11:516-528, 1966

19. Zakladu Z, Zwywnosci B, Uzthu P, et al: Semiquantitative method of determination of hydrogen cyanide in bitter and sweet almonds. Rocz Psh 24:703-705, 1973

20. Maxwell D: Increased cyanide values in a laetrile user. Can Med Assoc J 119:18, 1978

21. Niyogi SK: Drug levels in cases of poisoning. Forensic Sci 2:67-98, 1973

22. Naughton M: Acute cyanide poisoning. Anaesth Intensive Care 2:351-356, Nov 1974

23. Martindale W: The Extra Pharmacopoeia, 27th Ed. London, The Pharmaceutical Press, 1977, p 745

24. Dreisbach RH: Handbook of Poisoning, 8th Ed. Los Altos, CA, Lange Publishing, 1976, p 222

25. Arena JM: Poisoning, 4th Ed. Springfield, IL, Charles C Thomas, 1979, pp 34-35

26. Pedigo L: Antagonism between amyl nitrite and prussic acid. Med Soc Virginia 19:124-131, 1888

27. Geiger JC: Cyanide poisoning in San Francisco. JAMA 99:1944-1945, 1932

28. Chen KK, Rose CL, Glowes GA: Comparative values of several antidotes in cyanide poisoning. Am J Med Sci 188:767-781, 1934

29. Albaum HG, Tepperman J, Bodansky O: Competition of methemoglobin and cytochrome oxidase for cyanide in vitro. J Biol Chem 163:641-647, 1946

30. Berlin CM: The treatment of cyanide poisoning in children. Pediatrics 46:793-796, 1970

31. Bodansky O: Methemoglobinemia and methemoglobin-producing compounds. Pharmacol Rev 3:144-196, 1951

32. Conn JB, Norman SL, Wartman JG: The equilibrium between vitamin B12 (cyano-cobalamin) and cyanide ion. Science 113:658-659, 1951

33. Mushett CW, Kelley KL, Boxer GE, et al: Antidotal efficacy of vitamin B12 (hydroxocobalamin) in experimental cyanide poisoning. Proc Soc Exp Biol 81:234-237, 1952

34. Posner MA, Tobey RE, McElroy H: Hydroxocobalamin therapy of cyanide intoxication in guinea pigs. Anesthesiology 44:157-160, 1976

35. Yacoub M, Faure J, Morena H, et al: Acute cyanide poisoning, current data on the metabolism and treatment with hydroxocobalamine. Eur J Toxicol 71:22-29, Jan 1974

36. Evans CL: Cobalt compounds as antidotes for hydrocyanic acid. Br J Pharmacol 23:455-475, 1964

37. Isom G, Way JL: Cyanide intoxication: Protection with cobaltous chloride. Toxicol Appl Pharmacol 24:449-456, Mar 1973

38. Lovejoy FH Jr: Cyanide (Part II). Clin Toxicol Rev 2:Aug 1980

39. Burrows GE, Liu DH, Way JL: Effect of oxygen on cyanide intoxication V—Physiologic effects. J Pharmacol Exp Ther 184: 739-748, 1973